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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte VERNON C. MAINO and MARIA SUNI

Appeal 2007-4487
Application 08/803,702
Technology Center 1600

Decided: April 25, 2008

Before DEMETRA J. MILLS, ERIC GRIMES, and JEFFREY N. FREDMAN, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for lack of written description and lack of enablement. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Claim 19 is representative.

19. A method of detecting T lymphocytes that are specific for a nominal antigen, comprising:

culturing a sample containing peripheral blood mononuclear cells with a nominal antigen;

adding to said sample an inhibitor of cytokine secretion;

permeabilizing said cells;

adding to said sample at least one cytokine-specific antibody and at least one T lymphocyte subset-defining antibody; and then

flow cytometrically detecting the intracellular binding of said cytokine-specific antibody by cells in the defined T lymphocyte subset.

Cited Prior Art

Thomas Jung et al., "Detection of intracellular cytokines by flow cytometry," 159 *Journal of Immunological Methods*, 197-207 (1993).

Adi Elkeles et al., "Azide-resistant mutants in Acinetobacter calcoaceticus A2 are defective in protein secretion," 116 *FEMS Microbiology Letters*, 221-224 (1994).

Lynne H. Elson et al., "Flow Cytometric Analysis for Cytokine Production Identifies T Helper 1, T Helper 2, and T Helper 0 Cells Within the Human CD4+CD27^{-}Lymphocyte Subpopulation," 154(9) *The Journal of Immunology*, 4294-4301 (1995).

Louis J. Picker et al., "Direct Demonstration of Cytokine Synthesis Heterogeneity Among Human Memory/Effector T Cells by Flow Cytometry," 86(4) *Blood*, 1408-1419 (1995).

Calman Prussin et al., "Detection of intracytoplasmic cytokine using flow cytometry and directly conjugated anti-cytokine antibodies," 188 *Journal of Immunological Methods*, 117-128 (1995).

Philippe Robin et al., "Effect of microtubule network disturbance by nocodazole and docetaxel (Taxotere®) on protein secretion in rat extraorbital lacrimal and parotid glands," 67 *European Journal of Cell Biology*, 227-237 (1995).

Application Note 1, "Detection of Intracellular Cytokines in Activated Lymphocytes," Becton Dickinson and Co., 1-12 (1997).

Maria A. Suni et al., "Detection of antigen-specific T cell cytokine expression in whole blood by flow cytometry," 212 *Journal of Immunological Methods*, 89-98 (1998).

Nancy J. O'Neil-Andersen et al., "Differential Modulation of Surface and Intracellular Protein Expression by T Cells after Stimulation in the Presence of Monensin or Brefeldin A," 9(2) *Clinical and Diagnostic Laboratory Immunology*, 243-250 (2002).

Grounds of Rejection

1. Claims 19-24, 26-33, 35-38, 40-55 and 61-63 stand rejected under 35 U.S.C. § 112, first paragraph for lack of written description.

2. Claims 19-24, 26-33, 35-55 and 61-65 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

DISCUSSION

Background

The invention comprises an "approach to the assessment of antigen specific T cells [Ag-specific T cells] that quantitates and characterizes these cells with unprecedented clarity, and importantly, because it is performed in whole blood, is amenable to routine use in the clinical immunology laboratory." (Spec. 3.) "Evaluation of whole blood antigen specific cytokine responses has the important advantage of assessing T cell activation in the presence of ALL types of MHC autologous antigen presenting cells present in the native sample. It also has the advantage of

enabling a culture system (whole blood) which can reflect effects of systemic environments (i.e. drug augmentation or suppression) on T cell responses to specific stimuli including antigen by either culturing in the presence of such drug or analyzing the blood of a human or animal receiving such drug." (*Id.* at 3-4.)

"At its simplest, the methodology involves a step process, which involves culturing with the antigen specific stimulus and analyzing an aliquot of the cultured sample for expression of one or more intracellular cytokines and/or early activation antigens in combination with one or more T-cell markers, optionally with the lysing of the red blood cells and washing to remove debris." (*Id.* at 4.)

1. Claims 19-24, 26-33, 35-38, 40-55 and 61-63 stand rejected under 35 U.S.C. § 112, first paragraph for lack of written description.

The Examiner finds that

> [t]here is insufficient written description to show that Applicant was in possession of "an inhibitor of cytokine secretion" (Claim 19), other than Brefeldin A (BFA). The specification discloses no definition for said inhibitor and teaches only the single species, BFA. Absent any definition, the claim must be read broadly to include any chemical that could inhibit cytokine secretion, presumably including toxins ranging from benzene to sodium azide. Thus, the specification fails to adequately define the claimed invention and one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus.

(Ans. 4.)

> Appellants contend that
>
> the rejection is erroneous for the following reasons, …:
>
> 1. The use of an inhibitor of cytokine secretion to allow intracellular cytokines to accumulate, thereby facilitating the detection of the intracellular cytokines, was known at the time of the invention. The description need only describe in detail that which is new or not conventional.
>
> 2. The claims, read as a whole, are drawn to a new use of known compounds (an inhibitor of cytokine secretion) and are not drawn to either novel compounds per se or to methods using novel compounds. In such a case, the applicant is not required to discover all the compounds from this class that would be useable in the methods ([citing] In re Fuetterer …).
>
> The use of an "inhibitor of cytokine secretion" to facilitate detection of intracellular cytokines was known in the art.

(Br. 15-16.)

Appellants also put forth the publications of Jung, Elson, Prussin, Picker and Application Note 1 as evidence that the inhibitors of cytokine secretion, monensin and brefeldin-A, were known in the prior art. (Br. 16.)

"The 'written description' requirement [under 35 U.S.C. § 112, first paragraph] implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in

possession of the invention that is claimed." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). "The burden of showing that the claimed invention is not described in the application rests on the PTO in the first instance." *In re Edwards*, 568 F.2d 1349, 1354 (CCPA 1978). Moreover,

> the determination of what is needed to support generic claims to biological subject matter depends on a variety of factors, such as the existing knowledge in the particular field, the extent and content of the prior art, the maturity of the science or technology, the predictability of the aspect at issue, and other considerations appropriate to the subject matter.

Capon, 418 F.3d at 1359. For example, it is unnecessary for the specification to provide a description of proteins which are already known in the prior art. *Id.* at 1357-58.

In our view the preponderance of the evidence supports written description of the claimed invention. Appellants claim a method of detecting T lymphocytes that are specific for a nominal antigen. In one aspect the method employs known inhibitors of cytokine secretion for the known purpose of trapping the cytokine to allow for better flow cytometry detection. The Examiner argues that there are countless chemicals that can stop cytokine secretion and that O'Neil-Anderson evidences that the activity of inhibitors of cytokine secretion varies and the choice of a protein transport inhibitor is an important variable in assays. (O'Neil-Anderson, abstract.) Though this may be true, we are not persuaded by this argument. The Examiner's argument that the existence of predictably ineffective molecules which cause cell death does not subvert the disclosure of

two known effective molecules whose function is disclosed in the prior art.

While O'Neil-Anderson evidences that the activity of inhibitors of cytokine secretion varies, at the same time it supports Appellants' position that effective inhibitors of cytokine secretion were known in the art. We agree with Appellants that one of ordinary skill in the art would have known to select suitable inhibitors of cytokine secretion from those known in the prior art and find that the Appellants have presented sufficient disclosure to demonstrate that they were in possession of the invention that is claimed.

In view of the above, the rejection for lack of written description is reversed.

2. Claims 19-24, 26-33, 35-55 and 61-65 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

The Examiner contends that

> [e]lements critical or essential to the practice of the invention, but not included in the claims are not enabled by the disclosure. … Example 4 discloses additional required steps. For example, it is disclosed that a maximal response depended critically on the method being performed in slant tubes due to the geometry of the T cell/accessory cell interaction. The Example also discloses that the detection method of the instant claims also depended on "the inclusion of CD69 (not just any activation marker) assessment in the multiparameter protocol." Additionally, the Example discloses that the analysis "requires" the collection of at least 50,000 events. Most importantly, the specification and the post-filing art disclose/teach that the

> inclusion of an inhibitor of cytokine secretion is essential to the success of the claimed assay.

(Ans. 4-5.) Thus the Examiner relies on case law such as *In re Mayhew*, 527 F.2d 1229 (CCPA 1976), for the proposition that elements critical or essential to the practice of the invention but not included in the claims are not enabled by the disclosure. (Ans. 5.)

Appellants contend that these missing elements are not critical because they "represent preferred embodiments, e.g., elements that optimize, maximize or increase accuracy of the results, or elements that set for[th] the practical limits of operation." (Br. 25.) Appellants argue that the slant tubes taught in Example 4 are no more than a preferred embodiment of the invention as set forth in the Specification. (Br. 26.) In response to the Examiner's argument concerning critical elements are missing from the claims, Appellants further argue that

> [i]n determining whether an unclaimed feature is critical, the entire disclosure must be considered. Broad language in the disclosure (including the abstract) omitting, an allegedly critical feature tends to rebut the argument of criticality. Also, features that are merely preferred are not critical.

In re Goffe, 542 F.2d 564, 567 (CCPA 1976). (Br. 24.)

"[E]nablement requires that the specification teach those in the art to make and use the invention without 'undue experimentation' . . . That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is 'undue.'" *In re Vaeck*, 947 F.2d 488, 495 (Fed. Cir. 1991). The Examiner bears the initial burden of showing that a claimed invention is nonenabled. "[A] specification disclosure which

contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 439 F.2d 220, 223 (CCPA 1971). "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993).

We conclude that the Examiner has not set forth a reasonable explanation as to why it is believed that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the Specification of the application or why the practice of the claimed invention would require undue experimentation. For example, the Examiner has adduced no reason why substitution of other known containers for T cell culture medium such as roller bottles, culture dishes or bioreactors for slant tubes would not be expected to function. Similarly, there is no evidence that the 50,000 cell threshold has any particular significance other than the general expectation that more events will yield better statistical results. Nor do we find that the Examiner has established that the claimed method would have been wholly inoperative in the absence of the alleged critical elements. *Amgen Inc. v. Hoechst Marion Roussel Inc.*, 314 F.2d.

1313 (Fed. Cir. 2003.) It would reasonably appear from review of the disclosure that the elements which the Examiner alleges are critical to the claimed method are instead preferred embodiments of the practice of the claimed invention.

In view of the above, the rejection of the claims for lack of enablement is reversed.

SUMMARY

The enablement rejection is reversed. The written description rejection is reversed.

REVERSED

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